REMARKS

Claims 1-21 were pending at the time of the Office Action. Claims 1-13, 15, 18, and 19 stand withdrawn as drawn to non-elected subject matter. Claims 14 and 16 stand rejected under 35 U.S.C. § 101. Claim 16 stands rejected under 35 U.S.C. § 112, second paragraph. Claim 14 stands rejected under 35 U.S.C. §§ 102(a) and 102(b). Claims 14 and 17 stand rejected under 35 U.S.C. §§ 102(a) and 102(e). Claims 14, 16, 17, 20, and 21 stand rejected under 35 U.S.C. § 103(a). Applicants address each of these rejections below.

Amendments to the Claims

Claim 14 has been cancelled. Claim 16 has been rewritten in independent form and has been amended to feature an isolated mesenchymal cell comprising a minus-strand RNA viral vector encoding angiopoietin-1. Support for this amendment is found, e.g., on page 18, lines 10-13, and page 25, lines 6-31, of the English-language specification as filed. Claim 17 has been amended to feature the mesenchymal cell according to claim 16. In addition, new claims 22-25, featuring mesenchymal stem cells, have been added. Support for the new claims is found throughout the specification, e.g., on page 17, lines 27-29, of the English-language specification as filed.

The present amendments were made to expedite prosecution, and applicants reserve the right to pursue any cancelled subject matter in this or in a continuing

application. No new matter has been added.

Rejection Under 35 U.S.C. § 101

Claims 14 and 16 stand rejected under 35 U.S.C. § 101 as directed to non-statutory subject matter. The Office states (page 4):

> The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" before cells.

As suggested by the Office, applicants have amended claim 16 to recite the term "isolated." Applicants have also cancelled claim 14 and rewritten claim 16 in independent form. Accordingly, the rejection of claims 14 and 16 under 35 U.S.C. § 101 may now be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 16 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Office states (page 5):

> It is unclear if the claim is reciting a limitation of the vector encoding the foreign gene of claim 14, or if the genetically modified mesenchymal cell is transfected with a second vector encoding Ang-1, wherein the second vector is a minus-strand RNA viral vector, specifically a Sendai viral vector...the Examiner interprets the recitation of claim 16 to mean that the vector responsible for introducing the foreign Ang-1 gene is a minus-strand RNA viral vector.

The Office's interpretation is what is intended by applicants. Claim 16, as amended, is unambiguous; accordingly, the rejection under 35 U.S.C. § 112, second paragraph, should

be withdrawn.

Rejections Under 35 U.S.C. § 102

Claim 14 stands rejected under 35 U.S.C. § 102(a) as being anticipated by Nykanen et al. (Circulation 107:1308-1314, 2003). Claim 14 further stands rejected under 35 U.S.C. § 102(b) as being anticipated by Chae et al. (Arterioscler. Thromb. Vasc. Biol. 20:2573-2578, 2000). Claims 14 and 17 stand rejected under 35 U.S.C. §§ 102(a) and 102(e) as being anticipated by Ueno et al. (U.S. Application Publication No. 2002/0037278; "Ueno").

As noted above, claim 14 has been cancelled, and claim 17 has been amended to feature the mesenchymal cell according to claim 16, which has not been rejected under 35 U.S.C. § 102. Accordingly, the rejection of claims 14 and 17 under 35 U.S.C. §§ 102(a), 102(b), and 102(e) may now be withdrawn.

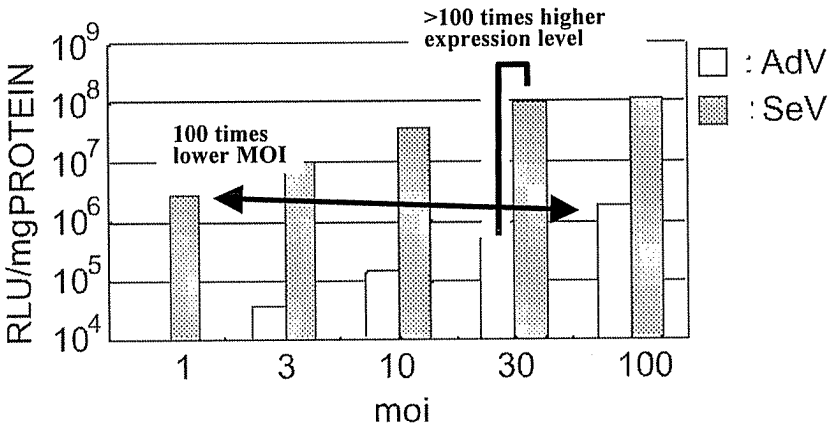
Rejection Under 35 U.S.C. § 103(a)

Claims 14, 16, 17, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ueno and Sakai et al. (FEBS Letters 456:221-226, 1999; "Sakai"). The Office states (page 8, emphasis added):

> It would have been obvious to one of ordinary skill in the art to substitute the viral vector of Ueno et al with a minus-strand RNA Sendai virus vector as taught be [sic] Sakai et al with a reasonable chance of success because the simple substitution of one viral vector for another would have yielded predictable results to one of ordinary skill in the art at the time of the

invention.

Applicants disagree. Selection of a minus-strand RNA viral vector, e.g., a Sendai virus vector, in the methods and compositions of the present invention would not have been obvious to one of skill in the art at the time of filing. In particular, the specification provides evidence of superior unexpected results using a minus-strand RNA viral vector, resulting in an overwhelming advantage over, e.g., an adenovirus vector in the context of gene transduction into mesenchymal cells. See, e.g., Example 14, pages 51-52 of the English-language specification as filed, entitled "Treatment of limb ischemia using the Ang1 gene-introduced mesenchymal cells." In particular, as shown in Fig. 16, the expression level of the transgene in mesenchymal stem cells infected with a minus-strand RNA viral vector at an MOI of 1 (i.e., one infectious virus particle per cell) was comparable to, or even higher than, that with an adenovirus vector at an MOI of 100. The expression level of the minus-strand RNA viral vector at an MOI of 30 was more than one hundred times higher than that of the adenovirus vector at the same MOI, as shown below in an annotated version of Fig. 16:



Regarding the above data, the specification states (page 52, lines 8-17, of the English-language specification as filed, emphasis added):

> The reporter gene was expressed at high levels even when the infection was performed with SeV at a low moi (3 moi or lower). The expression levels increased depending on the virus concentration, and nearly reached a plateau when moi was 30 or higher. In contrast, while the gene introduction into rat MSCs using the Ad vector was dependent on the virus concentration, the expression levels were low at any viral concentrations tested for comparison, and at a moi of 30 or lower the expression levels were one hundredth or less of that achieved with the SeV vector. MSCs, into which LacZ gene was introduced using the SeV vector or the Ad vector at a moi of 100, were stained with X-gal. As a result, the number of positive cells was relatively small when the Ad vector was used, but almost all cells were LacZ-positive with the use of the SeV vector (Fig. 17).

Accordingly, the specification demonstrates that the gene transduction efficiency of mesenchymal stem cells using a minus-strand RNA viral vector is extraordinarily, and unexpectedly, high. The mesenchymal stem cells into which the Ang-1 gene was introduced via a minus-strand RNA viral vector, when tested in a rat model, led to a significant improvement of the blood flow in the ischemic limbs (see, e.g., Fig. 18, and page 52, lines 18-31, of the English-language specification as filed). These results could not have been predicted from Ueno and Sakai, taken either alone or in combination. Indeed, contrast the teachings of the present specification, as presented above, with the teachings of Ueno, which states (page 6, paragraph [0048], emphasis added):

> The vector used in the methods of the present invention may be a viral vector, preferably a retroviral vector.

The disclosure of Ueno would lead a skilled artisan to use a retroviral vector rather than a

minus-strand RNA viral vector, meaning that the superiority of minus-strand RNA viral vectors such as Sendai virus in the context of mesenchymal cell expression, as demonstrated in the present application, was not at all obvious at the time of filing.

Even disregarding the results described in the present specification, applicants disagree with the Office's assertion, quoted above, that "simple substitution of one viral vector for another would have yielded predictable results." Ueno presents no results featuring mesenchymal cells into which the Angl gene has been introduced via a viral vector, nor any teaching of clinical effects resulting from the use of such cells. Thus, there is no basis for extrapolating predictable results in the first place, much less the superior unexpected results described in the present specification.

The Office additionally states (page 8, emphasis added):

> Furthermore, a minus-strand RNA viral vector is <u>not considered an essential feature of the invention</u> in light of the disclosure that the foreign gene encoding Ang-1 may also be delivered via non-minus-strand RNA viral vectors, e.g. an adenoviral vector, an adeno-associated viral vector, a retroviral vector, a lentiviral vector, a herpes simplex virus vector, and a vaccinia virus vector."

Applicants disagree. While vectors other than minus-strand RNA viral vectors are recited in the specification, the specification does <u>not</u> indicate that the expression level or efficacy of other vectors is comparable to that of minus-strand RNA viral vectors. Rather, the specification states (page 12, lines 26-29, of the specification as filed):

> As shown in the Examples, the minus-strand RNA viral vector could achieve higher expressions of an introduced gene with a lower titer than those of the adenovirus. The Angl-encoding minus-strand RNA viral vector is one of the most preferably used vectors in the present invention.

The specification further states (page 18, lines 10-13):

> In the present invention, minus-strand RNA viral vectors have been found to introduce foreign genes into mesenchymal cells with exceedingly high efficiency. Accordingly, when mesenchymal cells are used in an *ex vivo* administration, it is preferable to use a minus-strand RNA viral vector to introduce genes into the mesenchymal cells.

These teachings, and supporting data, stand in significant contrast with Ueno's preference for a retroviral vector. In any case, all claims, as amended, require a minus-strand RNA viral vector. Thus, based both on the data provided in the specification and on the claims as presently amended, applicants submit that the element of a minus-strand RNA viral vector is an inventive and essential feature of the presently claimed invention.

As a final matter, applicants note that the term "angiopoietin-1" appears on page 5 of Ueno as one of about thirty genes enumerated in paragraphs [0042] and [0043]. Ueno provides no working example of a genetically modified mesenchymal cell. Furthermore, Ueno does not demonstrate any effect of Ang1, or any of the other listed genes, on ischemia when expressed in mesenchymal cells. Without evidence, one skilled in the art could not have predicted whether the Ang1-expressing mesenchymal cells exhibit a therapeutic effect on ischemia. Specifically, a skilled artisan would not have predicted that the mesenchymal stem cells into which the Ang1 gene was introduced by a minus-strand RNA virus vector shows a significant therapeutic effect on ischemia. Thus, the Office's assertion (page 7, emphasis added) that "Ueno et al disclose that the nucleic acid molecule encoding the foreign gene may be introduced into the host mesenchymal cell

using anyone of a genus of viral vectors known in the art (pg 6, [0048])" fails to recognize either Ueno's clear preference for and teaching toward retroviral vectors, or the present specification's demonstration of superior unexpected results using a minus-strand RNA viral vector.

In view of the above arguments and the amendments to the claims, applicants respectfully request that the rejection of claims 14, 16, 17, 20, and 21 under 35 U.S.C. § 103(a) be withdrawn. New claims 22-25 depend from the preceding claims and are accordingly free of this basis of rejection as well.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Please charge $150.00 to Deposit Account No. 03-2095 in payment of additional claim fees for three excess claims at the time of electronic filing of this reply.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 1/31/2008

James D. DeCamp, Ph.D.
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045